REMARKS

Reconsideration of the rejections set forth in the Office action mailed October 19, 2004 is respectfully requested. Claims 1-4 are pending. Claims 5-12 and 15-20 were previously cancelled following restriction. Claims 13-14 are cancelled with this amendment.

I. Amendments

Claim 1 has been amended for clarification. Support for the designations of "polymorphic" and "non-polymorphic" are found, for example, in the description of Fig. 1 at page 6, line 19 to page 8, line 14 of the PCT specification, and particularly at page 7, lines 11-23 and page 8, lines 10-12.

Claim 1 has also been amended to recite that the pooled DNA is derived from at least five individuals, stated as a preferred embodiment at page 14, lines 21-24 of the PCT specification.

Support for the language "from digestion of said pooled DNA", regarding the fragments in the library, is found in the specification at page 14, lines 17-20.

Claims 13-14 are cancelled without prejudice.

No new matter is added by any of the amendments.

II. Drawings

Replacement sheets 1-19, including all of original Figures 1-11, are enclosed.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claim 1 and its dependent claims were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated, for example, that it was unclear how a fragment could be derived from a subregion of a theoretical sequence.

The claim has been amended to state that each of the fragments making up the reference library *has a sequence* that is either a portion of a polymorphic subregion of a polymorphic consensus sequence, or a non-polymorphic subregion of said consensus sequence. That is; the sequence of the fragment, not the fragment itself, is derived from the polymorphic

consensus sequence.

Similarly, the claim as amended recites that the *sequences of* the pooled DNA are aligned to provide maximum homology.

The "projecting" language of the claims has been deleted and replaced with language describing the designation of polymorphic and non-polymorphic subregions in the consensus sequence, per the description at pages 6-8 of the specification.

The Examiner also stated that the meaning of the claim term "enriched" was unclear.

The meaning of "enriched" or "enrichment" for fragments of type (a) relative to type (b) is defined in the specification at, for example, page 7, line 26 to page 8, line 10. Accordingly, fragments of type (a) are overrepresented in the library, relative to the consensus sequence, and fragments of type (b) are underrepresented. (See e.g. page 7, lines 28-29). (This does not require that there are more fragments of type (a) than (b) in the library, or vice versa.)

Because claims 13 and 14 have been cancelled, the rejection of these claims is moot.

In view of the foregoing, the applicants submit that amended claim 1 and its dependent claims comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §102(b)

Claims 1-3 and 13-14 were rejected under 35 U.S.C. §102(b) as being anticipated by Ausubel *et al.*, WO 95/25538. This rejection is respectfully traversed for the following reasons.

The applicant's invention, as embodied in independent claim 1, is directed to a nucleic acid reference library derived from pooled DNA from at least five individuals in a population, said library comprising a heterogeneous mixture of nucleic acid fragments from digestion of said pooled DNA.

The Examiner pointed in particular to Example XI in Ausubel *et al.*, illustrated in Fig. 9 of the publication. The collection of fragments produced in this Example does not comprise a mixture of fragments from digestion of "pooled DNA from *at least five individuals* in a population". The description of Example XI and the illustration in Fig. 9 clearly refer to "organism [or individual] A" and "organism [or individual] B".

Since the reference does not disclose all of the elements set out above in claim 1 and its independent claims, the claims cannot be anticipated by this reference under 35 U.S.C. §102(b). In view of this, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(b).

V. Rejections under 35 U.S.C. §102(a) and (b)

Claims 1, 13 and 14 were rejected under 35 U.S.C. §102(b) as being anticipated by Pierard *et al., J. Clin. Microbiol.* **36**(11):3317-22 (Nov 1998). This rejection is respectfully traversed for the following reasons.

The applicant's invention, as embodied in independent claim 1, is directed to:

a nucleic acid reference library derived from pooled DNA from at least five individuals in a population, said library comprising a heterogeneous mixture of nucleic acid fragments from digestion of said pooled DNA, wherein the sequence of each said fragment is either

(a) *a portion of a polymorphic subregion* of a polymorphic consensus sequence derived from said pooled DNA, or

(b) a non-polymorphic subregion of said polymorphic consensus sequence;

and said library is enriched for fragments of type (a) relative to type (b);

wherein said polymorphic consensus sequence is the sequence obtained by aligning the sequences of said pooled DNA to provide maximum homology, and said subregions of said polymorphic consensus sequence are defined by:

designating as "polymorphic", subregions which are bound on each end by a first restriction site s, present in each of said pooled DNA sequences, and which contain an internal second restriction site t, different from *said first restriction site*, in some but not all of said pooled DNA sequences, and

designating as "non-polymorphic", subregions which are bound on each end by said first restriction site s, and which contain said internal second restriction site t in either none or all of said pooled DNA sequences.

The Examiner states that Pierard *et al.* discloses a library of fragments in which each fragment is "a portion of a polymorphic subregion of a consensus sequence that are bounded

by first restriction sites..." (sentence bridging pages 8-9 of Office Action), and gives as an example a DNA segment containing the polymorphic restriction site PvuII (page 9 of Office Action).

The Examiner states that the polymorphic site in the fragment on page 9 is 'bounded by first restriction sites TseI...and EaeI".

However, this fragment differs from those in the claimed reference libraries in at least two respects. A polymorphic subregion, as defined in the claim, is "bound on each end by *a first restriction site s*" and "contain[s] an internal second restriction site t, different from *said first restriction site*". Accordingly, the "first restriction sites" of the claim are clearly the same site, not different sites (TseI and EaeI) as in the fragment shown on page 9.

Moreover, these two "first" sites (TseI and EaeI) are within the fragment. Therefore, even if the two sites were identical, the fragment could not be considered a polymorphic subregion, as defined in the claim, or "a portion of a polymorphic subregion"; it could at most be said to *contain* a polymorphic subregion.

Because claims 13 and 14 have been cancelled, the rejection of these claims is moot.

Since the reference does not disclose all of the elements set out above in independent claim 1, the claims cannot be anticipated by this reference under 35 U.S.C. §102(a) or (b). In view of this, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(a) and (b).

VI. Rejections under 35 U.S.C. §103

Claim 4 was rejected under 35 U.S.C. §103(a) as being unpatentable over Ausubel *et al.*, above, in view of Brenner, U.S. Patent No. 5,604,097. The rejections are respectfully traversed in light of the following remarks.

The applicant's invention, as embodied in claim 4, is directed to a nucleic acid reference library according to claim 2, wherein the oligonucleotide tags recited in claim 2 comprise oligonucleotides of the form:

$$S_1S_2S_3 \ldots S_n$$

wherein each of S_1 through S_n are subunits consisting of an oligonucleotide having a length

from 3 to 9 nucleotides and are selected from a minimally cross-hybridizing set, n is in the range of from 4 to 10, and said tag has a length in the range of from 12 to 60 nucleotides or base pairs.

The library of claim 2, in turn, is directed to a library according to claim 1, wherein at least a subpopulation of the nucleic acid fragments further comprise oligonucleotide tags, and different nucleic acid fragments are linked to different oligonucleotide tags.

The applicant notes that, if the "adaptors" in Fig. 9 of Ausubel are considered the "tags" of claim 2, as suggested by the Examiner, one cannot conclude that Ausubel shows or suggests such a library where "different nucleic acid fragments are linked to different oligonucleotide tags". For example, in Fig. 9C, each of four different fragments, designated 1', 2', 3' and 4', is linked to the same two adaptors (adaptor #1 and adaptor #2).

Moreover, Ausubel *et al.*, as described above, does not teach the library of claim 1, where the fragments are obtained from pooled DNA from at least five individuals. The library produced in Ausubel *et al.*, as described in Example 11 of the reference, can be used to locate a polymorphism in a first organism or sample which is not present in a second organism or sample (or vice versa). Ausubel does not teach how one would create a library which contains a "representation of the polymorphisms present in the population", as described in the applicants' specification at page 9, lines 3-5. As stated therein, "many individuals" are preferably represented in the applicant's library, to increase its representation of polymorphisms present in the given population. Accordingly, the present claims recite that the library is derived from pooled DNA of at least five individuals. This aspect is taught in neither of the cited references.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §103(a).

VII. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

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